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(71) Applicant: **THERAPICON SRL**
I-20146 Milan (IT)

(72) Inventors:
• **Veronesi, Paolo Alberto**
I-20146 Milano (MI) (IT)

• **Peschechera, Emanuela**
I-20125 Milano (MI) (IT)
• **Veronesi, Anna Maria**
I-06083 Bastia Umbra (PG) (IT)

(74) Representative: **Beszédes, Stephan G., Dr.**
Patentanwalt,
Münchener Strasse 80a
85221 Dachau (DE)

(54) **Pharmaceutical non-inorganic saline solutions for endonasal administration**

(57) The subject-matter of the invention are pharmaceutical non inorganic saline solutions for endonasal administration containing

a) a calcitonin, preferably salmon, as acetate salt,

characterized in that it further contains the organic excipients

b) N-(methyl)-glucamine,

c) tromethamine,

d) citric acid and

e) polyvinylpyrrolidone ranging from K15 to K120.

These are odourless and tasteless and thus have improved patient's compliance not having the undesirable secondary effects of known compositions as well as permit a complete and accurate analysis of the active principle and develop less degradation products during storage.

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Description

The invention is concerned with novel pharmaceutical non saline solutions for endonasal administration containing a natural or modified calcitonin, having enhanced organoleptic characters and a better patient's compliance.

Calcitonins are well-known long chain polypeptides used for convenient prophylaxis and therapy of some diseases, like Paget's disease, hypercalcemia and osteoporosis.

Calcitonin salmon is widely and efficiently adopted for the treatment of the above indications, so that specific monographs have been included in the most qualified pharmacopoeias, like Eur. Ph. II Ed., DAB 10 (1991), BP 88, F.U. IX Ed..

The above pharmacopoeias indicate that calcitonin salmon (dry active ingredient), as acetate salt, shall contain minimum 4,000 I.U. per milligrams (biological assay) and not more than 10% by weight of water and not more than 15% by weight of acetic acid. Storage condition at about 4°C/8°C is also prescribed for the powder stability.

Already there have been described saline compositions of calcitonin salmon for endonasal administration, which are stabilized with an appreciable quantity of acetic acid, but this presence results in that the entire composition develops remarkable unpleasant odour of acetic acid.

Additionally in the above compositions it is not possible to analytically establish the exact aliquot of acetic acid included in the active ingredient calcitonin (maximum 15% by weight) and the part of acetic acid, which has been added to the formulations as stabilizing excipient.

In other previous compositions (DE-A 33 35 086), hydrochloric acid has been used to adjust the pH value of the solution. This practice is also very inconvenient due to that hydrochloric acid is able to remove acetic acid from calcitonin acetate salt, thus determining an undesired liberation and odour of acetic acid.

Other publications teach that aliquots of calcitonins, for endonasal administration, therapeutically bioequivalent to those administered by parenteral route, are normally absorbed through the nasal mucosa and are also generally well tolerated. Calcitonins, specifically calcitonin salmon, as acetate salt, is remarkably unstable and, when it is not suitably formulated (bacterial contamination, pH exceeding 4.5, packed in non nitrogen atmosphere) or stored at temperatures above 8°C, it may develop some degradation products, which have already been described by some authors in the published literature.

In fact in same compositions (DE-A 33 35 086), benzalkonium chloride is used to avoid the bacterial contamination during the storage period and/or the utilization, but several studies have indicated that this preserving agent is able to produce some undesirable secondary effects (Am. J. Ophthalmol. 105 (6) [1988] pages 670 to 673; Contact Dermatitis 17 (1) [1987] pages 41 to 42; Cutis 39 (5) [1987] pages 381 to 383).

Thus the problem underlying to the invention is to create novel pharmaceutical solutions for endonasal administration containing a natural or modified calcitonin, preferably salmon, as acetate salt which are odourless and tasteless and thus has improved patient's compliance not having the undesirable secondary effects of known compositions as well as permit a complete and accurate analysis of the active principle and develop less degradation products during storage.

Surprisingly this has been attained by the invention.

The invention is based on the surprising recognition that non inorganic saline aqueous solutions containing natural or modified calcitonin as acetate salt (active principle) and besides water only organic excipients, described in the most common pharmacopoeias, like pharmaceutically acceptable acids, bases, suspending agents and, optionally C₁₋₄ alkylesters of p-hydroxybenzoic acid fulfil the above requirements. Surprisingly it has been found that such a composition as defined below is very suitable for endonasal administration, when applied to the nasal mucosa and it is odourless and tasteless, properties that improve the patient's compliance. Moreover it allows to perform a complete and accurate analysis of the active ingredient calcitonin salmon (including its volatile impurities, like acetic acid) and to minimize the profile of degradation products during the ageing period.

Hence the subject matter of the invention are pharmaceutical non inorganic saline solutions for endonasal administration containing

a) a natural or modified calcitonin, preferably salmon, as acetate salt,

characterized in that it further contains the organic excipients described in the most common pharmacopoeias

b) N-(methyl)-glucamine [meglumine],

c) tromethamine,

d) citric acid and

e) polyvinylpyrrolidone ranging from K15 to K120.

The active principle and the said organic excipients are dissolved in water.

Advantageously the calcitonin is human calcitonin, eel calcitonin, carbocalcitonin, chicken calcitonin or porcine calcitonin.

Preferably the polyvinylpyrrolidone is of the type K30.

Preferred solutions according to the invention contain

a) the calcitonin as acetate salt in concentration of 250 I.U./ml to 5,000 I.U./ml,

b) the N-(methyl)-glucamine in concentrations of 2.0 to 5.0 mg/ml,

c) the tromethamine in concentrations of 1.0 to 4.0 mg/ml,

d) the citric acid in concentrations of 5.0 to 9.0 mg/ml and

e) the polyvinylpyrrolidone ranging from K15 to K120 in concentrations of 5 to 25 mg/ml.

It is particularly preferred that the concentration of the calcitonin as acetate salt [a]) is from 500 I.U. to 1,200 I.U./ml.

Furthermore it is particularly preferred that the concentration of the N-(methyl)-glucamine [b]) is from 2.5 to 4.0 mg/ml.

Moreover it is particularly preferred that the concentration of the tromethamine [c]) is from 1.5 to 2.5 mg/ml.

It is also particularly preferred that the concentration of the citric acid [d]) is from 6.0 to 8.0 mg/ml.

Furthermore it is particularly preferred that the concentration of the polyvinylpyrrolidone ranging from K15 to K120 is from 8 to 15 mg/ml.

Moreover it is preferred the solutions according to the invention are sterile formulations.

According to an advantageous embodiment of the invention the solutions according to the invention contain 1 or more C₁₋₄ alkylester(s) of p-hydroxybenzoic acid [f]) for additional protection.

Preferably the C₁₋₄ alkylester(s) of p-hydroxybenzoic acid [f]) is/are methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate.

It is also preferred that the solutions according to the invention have pH values of from 3.0 to 5.0, particularly from 3.6 to 4.2.

A special particularly preferred solution according to the invention contains

550 I.U./ml of calcitonin salmon as acetate salt [a])

3.33 mg/ml of N-(methyl)-glucamine [b])

2.10 mg/ml of tromethamine [c])

6.82 mg/ml of citric acid [d])

10.00 mg/ml of polyvinylpyrrolidone K30 [e])

1.00 mg/ml of methyl p-hydroxybenzoate [f])

0.10 mg/ml of propyl p-hydroxybenzoate [f])

976.65 mg/ml of water for injectable preparations.

A further special particularly preferred solution according to the invention contains

1,077 I.U./ml of calcitonin salmon as acetate salt [a])

3.33 mg/ml of N-(methyl)-glucamine [b])

2.10 mg/ml of tromethamine [c])

6.82 mg/ml of citric acid [d])

10.00 mg/ml of polyvinylpyrrolidone K30 [e])

1.00 mg/ml of ethyl p-hydroxybenzoate [f])

0.10 mg/ml of propyl p-hydroxybenzoate [f])

976.65 mg/ml of water for injectable preparations.

By the solutions according to the invention the quality and the quantity of degradation products, during the storage period, is minimized. Thus they produce, during the ageing period of 18 months, only a very reduced quantity of the inactive degradation product hydroxy-calcitonin. Advantageously they present, after 18 months of shelf-life, a total quantity of degradation products substantially less than the 5% by weight limit indicated by various pharmacopoeias [Eur. Ph. II Ed., DAB 10 (1991), BP 88, FU IX Ed.] for calcitonin salmon substance. They are very suitable for endonasal administration, when dispensed in convenient well known delivery system.

The surprising advantages of the pharmaceutical solutions according to the invention summarized as follows:

A) The presence of citric acid [d]), useful to adjust the pH to values of from 3.0 to 5.0, particularly 3.6 to 4.2, allows to determine specifically and precisely, by using conventional analytical methods described in several publications, the exact quantity of acetic acid, contained as volatile impurity in calcitonin salmon.

In fact, if acetic acid was added to the solution instead of citric acid, it would not be possible to determine, in the formulated preparation, the quantity of the volatile impurity acetic acid (maximum 15% by weight) contained in calcitonin salmon.

B) The solution according to the invention with citric acid [d]) is organoleptically more acceptable to those patients, who don't tolerate the unpleasant odour of acetic acid, contained in some compositions on the market.

C) Citric acid [d]) has been partially buffered, in the solutions according to the invention, to pH 3.0 to 5.0, particularly 3.6 to 4.2, by using suitable concentrations of tromethamine [c]) and N-(methyl)-glucamine [b]) instead of sodium acetate, which can also develop a remarkable odour of acetic acid.

D) Polyvinylpyrrolidone ranging from K15 to K120, particularly K30 [e]) is purposely included into the composition for endonasal administration, since surprisingly it is suitable to prolong the time of contact between the solution and the nasal mucosa for its binding properties.

E) In the solutions of the invention, the presence of preserving agents is optional, because the manufacturing process is carried out to obtain sterile formulations. Moreover the nasal bottles are equipped with suitable pumps, characterized by absence of air introduction after actuation (dispensing the solution), eliminating, in this way, the possible bacteria contamination, during the usage. Therefore C₁₋₄ alkylesters of p-hydroxybenzoic acid, particularly methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate, [f]) are introduced into the solutions of the invention only for additional protection, in case of an exceptional presence of bacteria.

F) Various pharmacopoeias fix an individual limit of 5% by weight for each related substance {DAB (1991) "Verwandte Substanzen"; Eur. Ph. II Ed. "Substances apparentées"; BP 88 "Related substances"} for calcitonin salmon powder, as acetate salt, while other publications, more specifically Pharmaceutical Research Vol. 9, N. 11, 1992 ("Degradation of Synthetic Salmon Calcitonin in Aqueous Solution" - Kang Choon Lee, Yoon Joong Lee, Hyun Myo Song, Chang Ju Chun and Patrick P. DeLuca) indicate that the degradation product is only the reduced calcitonin salmon (dihydro-calcitonin), when the solution presents an acidic pH. Now surprisingly it has been found that the solutions of the invention produce only an inactive degradation product and minimize its quantity, during the ageing period of storage.

The described embodiments of the invention may apply also to other natural or modified calcitonins, alike human calcitonin, eel calcitonin, carbocalcitonin, chicken calcitonin, porcine calcitonin.

The solutions according to the invention can be administered as drops, inhaler or spray, dispensed in suitable well known delivery systems.

The invention is further illustrated by the following examples.

Example 1

Preparation of 25,000 bottles (2.0 ml) of calcitonin salmon nasal spray 50 I.U./actuation

Each actuation dispensing 90 µl of solution (50 I.U. of active principle) 1 ml of the solution containing the following constituents:

Ingredient	Amount
Calcitonin salmon as acetate salt	550 I.U.
N-(Methyl)-glucamine	3.33 mg
Tromethamine	2.10 mg
Citric acid (pH 3.6 to 4.2)	6.82 mg
Polyvinylpyrrolidone K30	10.00 mg
Methyl p-hydroxybenzoate	1.00 mg
Propyl p-hydroxybenzoate	0.10 mg
Water for injectable preparations	976.65 mg

The manufacturing process is carried out with the following conventional steps:

α) 38.0 kg of water for injectable preparations are introduced in a stainless steel dissolutor.

β) In about 3 litres of water are separately prepared two solutions containing:

solution A:	105.0 g of tromethamine + 165.0 g of citric acid
solution B:	166.5 g of N-(methyl)-glucamine + 163.5 g of citric acid.

γ) Once the above solutions have been completely dissolved, they are added to the water in the dissolutor.

δ) Under constant and slow stirring, 500.0 g of polyvinylpyrrolidone K30, 50.0 g of methyl p-hydroxybenzoate and 5.0 g of propyl p-hydroxybenzoate and, finally, the remaining quantity of citric acid (12.5 g) are added to yield the pH value of 3.6 to 4.2.

ε) Separately 27.50×10^6 I.U. of calcitonin salmon as acetate salt are dissolved in about 50 ml of solution, resulting from step γ) thus obtaining the mother solution.

ζ) Under constant and slow stirring, the mother solution of calcitonin salmon and the remaining quantity of water are added to the dissolutor to yield 50 kg.

All manufacturing steps from α) to ζ) are carried out under nitrogen atmosphere at positive pressure.

The obtained solution is filtered for sterilization and subsequently bottled under nitrogen atmosphere at positive pressure according to the well-known methods in the Art.

Example 2

Preparation of 38,461 bottles (1.3 ml) of calcitonin salmon nasal spray 100 I.U./actuation

Each actuation dispensing 90 µl of solution (100 I.U. of active principle) 1 ml of the solution containing the following constituents:

Ingredient	Amount
Calcitonin salmon as acetate salt	1,077 I.U.
N-(Methyl)-glucamine	3.33 mg
Tromethamine	2.10 mg
Citric acid (pH 3.6 to 4.2)	6.82 mg
Polyvinylpyrrolidone K30	10.00 mg
Methyl p-hydroxybenzoate	1.00 mg
Propyl p-hydroxybenzoate	0.10 mg
Water for injectable preparations	976.65 mg

The manufacturing process is carried out with the following conventional steps:

α) 38.0 kg of water for injectable preparations are introduced in a stainless steel dissolutor.

β) In about 3 litres of water are separately prepared two solutions containing:

solution A: 105.0 g of tromethamine + 165.0 g of citric acid

solution B: 166.5 g of N-(methyl)-glucamine + 163.5 g of citric acid.

γ) After the complete dissolution of these solutions they are added to the water in the dissolutor.

δ) Under constant and slow stirring, 500.0 g of polyvinylpyrrolidone K30, 50.0 g of methyl p-hydroxybenzoate and 5.0 g of propyl p-hydroxybenzoate and, finally, the remaining quantity of citric acid (12.5 g) are added to yield the pH value of 3.6 to 4.2.

ε) Separately a mother solution of calcitonin salmon as acetate salt is prepared by dissolving 53.85×10^6 I.U. of this active principle in about 50 ml of solution resulting from step γ).

ζ) Under constant and slow stirring, the mother solution of calcitonin salmon and the remaining quantity of water are added to the dissolutor to yield 50 kg.

All manufacturing steps from α) to ζ) are carried out under nitrogen atmosphere at positive pressure.

The obtained solution is sterilized and bottled under nitrogen atmosphere at positive pressure according to the well-known methods in the Art.

Example 3

Stability study of calcitonin salmon nasal spray preparations of Examples 1 and 2

The stability study is carried out comparing the pharmaceutical solution according to the invention of Examples 1 and 2 to two formulations available on the market, in order to assess the quality and the quantity of degradation products, during an interval of 18 months at the controlled storage temperature of $+2^{\circ}/+8^{\circ}\text{C}$.

Formulations I and II are those indicated in Examples 1 and 2, while the compared formulations C and D have the following compositions:

Formulation III: 1 ml of solution containing 550 I.U. of calcitonin salmon as acetate salt, 0.002 g of glacial acetic acid, 0.002 g of sodium acetate trihydrate, 0.0075 g of sodium chloride and water for injectable preparations q.s. to 1 ml.

Formulation IV: 1 ml of solution containing 550 I.U. of calcitonin salmon as acetate salt, 0.1 mg of benzalkonium chloride, 8.5 mg of sodium chloride, 4 mg of 0.1 N hydrochloric acid and 990.025 mg of bidistilled water.

The obtained results are summarized in the following Table 1.

Table 1

	TIME 0 (Initial)		AFTER 18 MONTHS	
Formulation	Degradation products			
	hydroxy -calci- tonin % by weight	dihydro -calcitonin % by weight	hydroxy -calci- tonin % by weight	dihydro -calcitonin % by weight
Formulation I (Example 1)	0.11	0	1.87	0%
Formulation II (Example 2)	0.13	0	2.14	0%
Formulation III	0.10	0	4.31	2.58
Formulation IV	0.12	0	5.06	2.37

As it may be taken from the above results, the pharmaceutical formulations of the invention (I und II) generate, during the considered ageing period of 18 months, remarkably minor quantities of the inactive degradation product hydroxy-calcitonin, compared to reference formulations III and IV which additionally produce another related substance indicated as dihydro-calcitonin (reduced calcitonin).

Example 4

Comparative study of organoleptic characters of the pharmaceutical formulations I (according to the invention) and III (reference) of Example 3

In order to assess the tolerability and compliance of the considered preparations, a comparative double-blind study between the pharmaceutical formulation I (according to the invention) and II (reference) of Example 3 has been carried out, by administering them to a total of 20 healthy and non smoking volunteers, divided into two groups.

In phase 1 test, 10 volunteers have inhaled formulation I while the second group formulation III. Phase 2 test was carried out, after two hours interval, by administering to the first group formulation III and to the second group formulation I.

The obtained results are summarized in the following Tables 2 and 3.

Table 2

Phase 1 Test		
Organoleptic evaluation	Formulation I	Formulation III
Odour of acetic acid	0	7
Odourless	9	1
No difference	1	2

Table 3

Phase 2 Test		
Organoleptic evaluation	Formulation I	Formulation III
Odour of acetic acid	0	9
Odourless	8	0
No difference	2	1

It results from the above Tables 2 and 3 that most of the treated volunteers of the two groups (16) have reported that formulation III (reference) has a statistically significant unpleasant odour of acetic acid, while 17 volunteers have not detected any specific odour in formulation I (according to the invention).

Claims

1. Pharmaceutical non inorganic saline solutions for endonasal administration containing
 - a) a natural or modified calcitonin, preferably salmon, as acetate salt,
 characterized in that it further contains the organic excipients
 - b) N-(methyl)-glucamine,
 - c) tromethamine,
 - d) citric acid and
 - e) polyvinylpyrrolidone ranging from K15 to K120.
2. Pharmaceutical solutions according to claim 1, characterized in that the calcitonin is human calcitonin, eel calcitonin, carbocalcitonin, chicken calcitonin or porcine calcitonin.
3. Pharmaceutical solutions according to claim 1 or 2, characterized in that the polyvinylpyrrolidone is of the type K30.
4. Pharmaceutical solutions according to claims 1 to 3, characterized in that they contain
 - a) the natural or modified calcitonin as acetate salt in concentrations of 250 I.U./ml to 5.000 I.U./ml,
 - b) the N-(methyl)-glucamine in concentrations of 2.0 to 5.0 mg/ml,
 - c) the tromethamine in concentrations of 1.0 to 4.0 mg/ml,
 - d) the citric acid in concentrations of 5.0 to 9.0 mg/ml and
 - e) the polyvinylpyrrolidone ranging from K15 to K120 in concentrations of 5 to 25 mg/ml.
5. Pharmaceutical solutions according to claims 1 to 4, characterized in that the concentration of the natural or modified calcitonin as acetate salt [a]) is from 500 I.U. to 1,200 I.U./ml.
6. Pharmaceutical solutions according to claims 1 to 5, characterized in that the concentration of the N-(methyl)-glucamine [b]) is from 2.5 to 4.0 mg/ml.
7. Pharmaceutical solutions according to claims 1 to 6, characterized in that the concentration of the tromethamine [c]) is from 1.5 to 2.5 mg/ml.

8. Pharmaceutical solutions according to claims 1 to 7, characterized in that the concentration of the citric acid [d]] is from 6.0 to 8.0 mg/ml.
9. Pharmaceutical solutions according to claims 1 to 8, characterized in that the concentration of the polyvinylpyrrolidone ranging from K15 to K120 is from 8 to 15 mg/ml.
10. Pharmaceutical solutions according to claims 1 to 9, characterized in that they are sterile formulations.
11. Pharmaceutical solutions according to claims 1 to 10, characterized in that they also contain 1 or more C₁₋₄ alkylester(s) of p-hydroxybenzoic acid [f]] for additional protection.
12. Pharmaceutical solutions according to claims 1 to 11, characterized in that the C₁₋₄ alkylester(s) of p-hydroxybenzoic acid [f]] is/are methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate.
13. Pharmaceutical solutions according to claims 1 to 12, characterized in that they have pH values of from 3.0 to 5.0.
14. Pharmaceutical solutions according to claims 1 to 13, characterized in that they have pH values of from 3.6 to 4.2.
15. Pharmaceutical solutions according to claims 1 to 14, characterized in that they contain
 - 550 I.U./ml of calcitonin salmon as acetate salt [a]]
 - 3.33 mg/ml of N-(methyl)-glucamine [b]]
 - 2.10 mg/ml of tromethamine [c]]
 - 6.82 mg/ml of citric acid [d]]
 - 10.00 mg/ml of polyvinylpyrrolidone K30 [e]]
 - 1.00 mg/ml of methyl p-hydroxybenzoate [f]]
 - 0.10 mg/ml of propyl p-hydroxybenzoate [f]]
 - 976.65 mg/ml of water for injectable preparations
16. Pharmaceutical solutions according to claims 1 to 15, characterized in that they contain
 - 1,077 I.U./ml of calcitonin salmon as acetate salt [a]]
 - 3.33 mg/ml of N-(methyl)-glucamine [b]]
 - 2.10 mg/ml of tromethamine [c]]
 - 6.82 mg/ml of citric acid [d]]
 - 10.00 mg/ml of polyvinylpyrrolidone K30 [e]]
 - 1.00 mg/ml of methyl p-hydroxybenzoate [f]]
 - 0.10 mg/ml of propyl p-hydroxybenzoate [f]]
 - 976.65 mg/ml of water for injectable preparations
17. Pharmaceutical solutions according to claims 1 to 16, characterized by that they allow to determine precisely, by using conventional analytical methods, the exact quantity of acetic acid contained, as volatile impurity, in calcitonin salmon active ingredient or any other natural or modified calcitonin as acetate used for their preparation.
18. Pharmaceutical solutions according to claims 1 to 17, characterized in that they have enhanced organoleptic characters and show improved patient's compliance, where citric acid [d]], N-(methyl)-glucamine [b]] and tromethamine [c]] are used instead of acetic acid and sodium acetate.
19. Pharmaceutical solutions according to claims 1 to 18, characterized in that polyvinylpyrrolidone in a range from K15 to K120, preferably polyvinylpyrrolidone K30, [e]] is suitable, for its binding properties, to prolong the time of contact between the solution and the nasal mucosa.
20. Pharmaceutical solutions according to claims 1 to 19, characterized in that they minimize the quality and the quantity of degradation products, during the storage period.
21. Pharmaceutical solutions according to claims 1 to 20, characterized in that they produce, during the ageing period of 18 months, only a very reduced quantity of the inactive degradation product hydroxy-calcitonin.
22. Pharmaceutical solutions according to claims 1 to 21, characterized in that they present, after 18 months of shelf-life, a total quantity of degradation products substantially less than the 5% by weight limit indicated for each impurity

(related substance) by various pharmacopoeias [Eur. Ph. II Ed., DAB 10 (1991), BP 88, FU IX Ed.] for calcitonin salmon substance.

23. Pharmaceutical solutions according to claims 1 to 22, characterized in that they are very suitable for endonasal administration, when dispensed in convenient well-known delivery system.

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EUROPEAN SEARCH REPORT

Application Number
EP 95 10 1681

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 122 036 (TEIJIN LTD) 17 October 1984 * page 8, line 14 - line 30 * * claims 1,7,14 * ---	1	A61K38/23 A61K9/06
A	WO-A-93 06854 (SMITH KLINE BEECHAM FARMACEUTICI SPA) 15 April 1993 * page 17 - page 18; examples 19,20 * ---	1	
A	EP-A-0 358 234 (RORER INTERNATIONAL (OVERSEAS) INC) 14 March 1990 * page 12, line 13 - line 20 * * page 13; example 8 * ---	1	
A	EP-A-0 490 549 (CIBA-GEIGY AG) 17 June 1992 * page 2, line 44 - line 45 * * page 3; example 1 * * page 5; example 4 * ---	1	
		-/--	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	7 August 1995	Boulois, D	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 Columbus, Ohio, US; abstract no. 97319, NOGATA YOSHIHIKO ET AL 'AQUEOUS COMPOSITIONS CONTAINING CALCITONINS' * abstract *	1	
A	& DATABASE WPI Section Ch, Week 9211 Derwent Publications Ltd., London, GB; Class B04, AN 92-85873 & JP-A-04 029 938 (TOYO JOZO KK) , 31 January 1992 * abstract *	1	
A	& PATENT ABSTRACTS OF JAPAN vol. 16 no. 194 (C-938) ,11 May 1992 & JP-A-04 029938 (TOYO JOZO CO LTD) 31 January 1992, * abstract *	1	
A	EP-A-0 504 483 (PULITZER ITALIANA SPA) 23 September 1992 * page 4 - page 5; example 6 * -----	1	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
Place of search THE HAGUE		Date of completion of the search 7 August 1995	Examiner Boulois, D
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 (03.91) (PACH)